to access Applicant's Deposit Account No. 08-3255 and advise Applicant upon doing so.

The Examiner has in effect allowed the 300 mg dosage form as providing unexpected utility over the prior art based on the submissions in the last response as discussed with Examiner Pulliam about June 3, 2001. The Examiner, having concluded that Claim 40 contains allowable subject matter, must have accepted the data provided in our last response. As the Examiner will recall, she cited EPA 856 313 (**'313**) and WO 93/00 093 (**'093**) (Goeghegan and Deboeck, respectively) against the application. The Examiner, at page 5 of the last Official Action, with respect to the EPA '313, stated:

> Additionally, applicant has submitted data, and claims unexpected results in order to overcome the rejection under 35 U.S.C. 103(a). The examiner has thoroughly considered the submitted data and declarations, and finds them to be persuasive only for a 300 mg capsule, as that is the only dosage form discussed in the comparison. Excluding claim 40, none of the above rejected claims are commensurate in scope with the data provided.

With respect to WO '093, the Examiner stated as follows:

> Furthermore, applicant argues that the peak to trough variance for the WO '093 reference (which corresponds to Tiazac) is much larger than that of applicant's formulation. Applicant has provided evidence to reinforce this statement. However, the examiner respectfully disagrees as the data regarding Tiazec is concerning a 240 mg formulation, and the data regarding applicant's claimed formulation is based on a 300 mg capsule. Therefore, this comparison is not persuasive, and the rejection is maintained.

It is therefore clear that with appropriate data and submissions, the Examiner would be prepared to consider the allowability to allow all of the other dosage form claims.

With respect to the other dosage forms, Applicant submits that for the same reasons the Examiner has indicated the allowability of the claims in respect of the 300 mg dosage form, the Examiner should allow the claims in respect of all the

dosage forms. The bases are – scientific analysis and determination and Pharmacokinetic testing.

The Examiner will recall that submissions were made by Applicant in respect of "Peak to Trough Variation". This characteristic is also identified as the "Degree of Fluctuation". The "Degree of Fluctuation" can be determined both scientifically by analyzing data in accordance with scientific principles and calculations and by testing, both pharmacokinetic and clinical.

1) Scientific demonstration:

The Degree of Fluctuation (% Fluct.) is a true measure of the "Peak to Trough Variation". The % Fluct. is a common measure obtained from Pharmacokinetic studies called Biovailaibility or bioequivalence studies; it can also be computed using FDA's scientific criteria for determining the Degree of Fluctuation (% Fluct.). See Schedule 1. (Schedule 1 - %Fluct.) This calculation or determination is based on the difference between the Maximal Plasma concentration (Cmax.) and the Minimum plasma concentration (Cmin.) divided by the average concentration during dosing interval. According to the scientific community, the Degree of Fluctuation should be determined in accordance with Schedule 2 (Schedule 2 =%Swing) using the better and more accurate formula (and preferred formula where the maximal plasma level difference is divided by the Cmin). The Examiner will appreciate that when solving the equations (both in Schedules 1 and 2) and substituting for known elements, when solving the equation for determining "Degree of Fluctuation" (Peak to Trough Variation) is DOSE INDEPENDENT. The Degree of Fluctuation is dependent only on absorption and elimination rates (contributed by the characteristics of the dosage) and the dosing interval but not the dose itself.

The two Schedules (1 and 2) represent a mathematical demonstration of the determination that there is no Dose factor in determining the % Fluct. from

the equations. (The basic pharmacokinetic equations were extracted from the Reference Book edited by Milo Gibaldi and Donald Perrier in 1976 (excerpt attached as Schedule 3).)

The Examiner will therefore now appreciate why Applicant submitted that the earlier submissions applied to all of the dosages claimed herein.

2) Pharmacokinetic Test Results

To assist the Examiner further, Applicant encloses the results of a Steady State Pharmacokinetic dose ranging study. (See Schedule 4: Study #1821.) Unlike other commonly measured parameters such as AUC (Area Under The Curve) and Cmax (Maximal Concentration), the % Fluct. for the dosages as confirmed by these results remains constant (within experimental limits).

The Diltiazem % Fluct. found were respectively, 114.74% for the 120 mg strength, 108.23% for the 240 mg strength and 114.55% for the 300 mg strength of Diltiazem. These values are consistent with both the scientific calculations (both FDA's calculations and the scientific community's calculations).

As expected the same conclusion is also reached for the active metabolites Deacetyldiltiazem and Desmethyldiltiazem. (See also Schedule 4.) It is therefore clear that the science confirms the Pharmacokinetics and the Pharmacokinetic testing confirms the science.

As discussed with the Examiner, the Examiner will recall that in the first Official Action the Examiner required Applicant to elect between tablets and capsules until at least one generic claim was allowed. The said at least one generic claim, in Applicant's respectful submission, has been allowed. Applicant therefore requests the Examiner to withdraw the restriction of the case to capsules and to therefore have this case apply to both capsules and tablets (to save Applicant the expense of filing the same case with respect to tablets).

Applicant's agent has reviewed the setting down of the telephone interview with the Examiner and generally agrees with the Statements of the Examiner except that Applicant's Agent believes he stated that the variance in the formulations in this case were at least as low as the prior art and lower (smaller).

Attached hereto as **Exhibit A** is a marked-up version of the changes made to the claims by the present amendment. Exhibit A is entitled "EXHIBIT A - CLAIMS WITH MARKINGS TO SHOW CHANGES".

Attached hereto as **Exhibit B** is a clean set of all pending claims following entry of this amendment. Exhibit B is entitled: "EXHIBIT B - CLEAN SET OF ALL PENDING CLAIMS FOLLOWING ENTRY OF THE PRESENT AMENDMENT". All of the currently pending claims are consolidated in this list for the convenience of the Examiner.

All changes and amendments have been made to further clarify Applicant's invention and not in accordance with any statutory requirements.

In view of the above submissions, Applicant respectfully submits that the Application is in condition for allowance and same is solicited at the earliest convenience.

If the Examiner has any questions, the Examiner is respectfully requested to contact Applicant's Agent, Ivor M. Hughes, or Marcelo K. Sarkis, at (905) 771-6414 (collect) at the Examiner's convenience.

Respectfully submitted,

Marcelo Sarkis
Registration #37,015
Agent for Applicant

IMH/mse
Enclosures
1. Exhibit A (Pending Claims with Markings);
2. Exhibit B (Clean Set of Pending Claims);
3. Schedule 1;
4. Schedule 2;
5. Schedule 3;
6. Schedule 4;
7. Requisition for a Three-Month Extension of Time;
8. Cheque in the amount of $920.00 USD;
9. Cheque in the amount of $864.00 USD.